Remarks

Reconsideration of this Application is respectfully requested.

The foregoing amendments to the specification are sought to provide proper cross-reference to the priority information for this application and to correct the sequence identifiers. Therefore, these amendments do not add new matter.

Upon entry of the foregoing amendment, claims 53-93 are pending in the application, with 53, 64, 65, 73, 83, 88 and 93 being the independent claims. Claims 1-52 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 53-93 are sought to be added. Support for the new claims can be found in the original claims as filed and throughout the specification. Specifically, support can be found at page 4, line 26 to page 5, line 3; page 7, lines 25-30; page 22, lines 3-5; page 23, lines 8-11; pages 25-29; page 32, lines 3-18; page 34, lines 9-22; page 35, lines 23-25; page 38, lines 23-36; and page 39, lines 1-19. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

A. Objection for Lack of Compliance with the Sequence Rules

In the Office Action at page 3, the Examiner states that the sequence listing filed on January 11, 2000, fails to comply with 37 C.F.R. §§ 1.821-1.825, because certain sequence identifiers in the specification, notably at page 81, line 17; page 49, line 17; and page 56,

line 27, are incorrect. Applicants have made an amendment to the specification correcting such errors. Applicants have also reviewed the specification for other occurrences of this error and have found none. Accordingly, Applicants respectfully request the withdrawal of the objection.

B. Objection to the Claims

In the Office Action at page 4, the Examiner objected to claims 1, 14, 16, 21 and 22 because of informalities. By the foregoing amendment, these claims have been cancelled. Therefore, objection to these claims is rendered moot. New claims 53-93 do not contain these errors. Accordingly, Applicants respectfully request the reconsideration and withdrawal of the objection.

C. Rejection under 35 U.S.C. § 101

In the Office Action at page 4, the Examiner rejected claim 16 under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. By the foregoing amendment, claim 16 has been cancelled. Corresponding new claims 61 and 80 are directed to a *transfected* host cell comprising the isolated polynucleotides of the invention, as suggested by the Examiner. In view of the above, Applicants respectfully request the reconsideration and withdrawal of the rejection.

D. Rejection under 35 U.S.C. § 112, First Paragraph

In the Office Action at pages 5-9, the Examiner rejected claims 1, 2, 6, 7, 9, 10 and 12-23 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled by the specification. Specifically, the Examiner stated that the specification

> does not reasonably provide enablement for an isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence that is at least 65% but less than 100% identical to SEQ ID NO:1, the complement or a fragment of said nucleic acid molecule, an isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence that is at least 65% but less than 100% identical to a nucleotide sequence encoding the polypeptide of SEQ ID NO:2, a vector comprising a nucleic acid molecule comprising a polynucleotide having a nucleotide sequence that is at least 65% but less than 100% identical to SEQ ID NO:1, a host cell comprising said vector, a method for producing a polypeptide comprising culturing said host cell, an isolated polypeptide comprising an amino acid sequence at least 65% identical but less than 100% identical to SEQ ID NO:2, and an antigenic fragment of said polypeptide.

(Paper No. 13, page 5.) Applicants respectfully traverse this rejection.

The Examiner has stated that "the claimed invention encompasses a much broader genus of isolated nucleic acid molecules having undisclosed polynucleotide sequences." (Paper No. 13, page 6.) Applicants note that claims 1-52 have been cancelled in favor of new claims 53-93. The new claims are generally directed to nucleic acids encoding polypeptides that are 95% identical to a mouse or human *tag7* protein, nucleic acids that are at least 95% identical to the gene encoding human *tag7*, and polypeptides that are 95% identical to a mouse or human *tag7* protein. Thus, the Examiner's remarks with respect to a "broad genus" are inapplicable to the present claims because the polynucleotides and polypeptides are narrowed to at least 95% identical.

The Examiner also states that "the specification does not teach which amino acid residues are critical to the function of the protein comprising SEQ ID NO:2, and moreover, does not teach which amino acids can be used to replace critical residues in the protein so that the resultant protein retains the function of the protein comprising SEQ ID NO:2." (Paper No. 13, page 7.) Applicants respectfully disagree. Contrary to the Examiner's assertions, the specification does in fact disclose regions of the protein which are important to the function of the claimed nucleic acid molecules and encoded proteins. For example, one function of the claimed protein is to raise antibodies against *tag7*. (*See* Specification, page 35, lines 22-32.) To that end, the specification discloses predicted antigenic regions of the mouse *tag7* polypeptide — specifically, the specification teaches that nucleic acid molecules which encode epitope-bearing portions of the mouse *tag7* polypeptide include polynucleotides which encode amino acids 20 to 40 of (SEQ ID NO:2); amino acids 55 to 75 of SEQ ID NO:2; amino acids 90 to 100 of SEQ ID NO:2; and amino acids 145 to 160 of SEQ ID NO:2. (*See* Specification, page 23, lines 2-13.) Provided with the predicted antigenic regions of the mouse *tag 7* polypeptide, one of ordinary skill in the art would know to minimize, or altogether avoid making substitutions, insertions and/or deletions in the disclosed regions in order to produce a protein that is at least 95% identical to mouse *tag 7*. Other structurally significant portions of the protein are vividly depicted in Figure 2. Thus, Applicants have provided sufficient guidance as to which amino acid substitutions, deletions and/or insertions could be made without changing the function of the protein, at least with respect to producing anti-*tag 7* antibodies. Accordingly, it would not require undue experimentation to produce variants within the scope of the claims.

Moreover, Applicants' specification teaches that:

> [i]t will be recognized by those of ordinary skill in the art that some amino acid sequences of the *tag7* polypeptide can be varied without significant effect on the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine structure and activity. In general, it is possible to replace residues which form the tertiary structure, provided that residues performing a similar function are used. In other instances, the type of residue may be completely unimportant if the alteration occurs at a non-critical region of the polypeptide.

(Specification, page 30, lines 23-31.) Furthermore, the specification teaches that:

> [s]uch mutants may include deletions, insertions, inversions, repeats, and type substitutions (for example, substituting one hydrophilic residue for another, but not strongly hydrophilic for strongly hydrophobic as a rule). Small changes or such "neutral" amino acid substitutions will generally have little effect on activity.

and that:

> [t]ypical conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxylated residues Ser and Thr; exchange of the acidic residue Asp and Glu; substitution between the amidated residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr.

(Specification, pages 30, lines 35-36 and page 31, lines 1-9.) Accordingly, Applicants have provided ample guidance to one of ordinary skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation.

To further support the rejection, the Examiner has also stated:

> [w]ith each and every discrepant nucleotide residue, the predictability that the claimed nucleic acid molecule will function similarly enough to the isolated nucleic acid comprising SEQ ID NO:1 for this instant disclosure declines significantly. In fact, even a single nucleotide alteration in a polynucleotide sequence can result in the alteration the amino acid sequence of a protein, and even a single alteration in the

> amino acid sequence of a protein can drastically alter the function of the protein.

(Paper No. 13, page 6.) The Examiner cites Bowie *et al.*, *Science 257*:1306-1310 (1990), Burgess *et al.*, *J. Cell Biol. 111*:2129-2138 (1990), and Lazar *et al.*, *Mol. & Cell. Biol. 8*:1247-1252 (1988) to support this assertion.

Applicants believe that the Examiner has overlooked all of what Bowie *et al.* teach. Specifically, Bowie *et al.* note that the "message [for encoding proteins] is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity"; and that "proteins are surprisingly tolerant of amino acid substitutions." Moreover, Applicants submit that the teachings of Burgess *et al.* and Lazar *et al.* are the exceptions that prove the rule. As a specific example, Applicants direct the Examiner's attention to the beta subunit of hemoglobin. It has been established that the majority of amino acid substitutions within the beta subunit of hemoglobin are functionally "silent." *See, e.g.,* Hutt *et al. Hemoglobin 20(4)*:371-6 (1996) ("Approximately 700 hemoglobin variants have been reported, causing a variety of clinical manifestations, with the majority being clinically silent."). *See also* Arous *et al., FEBS Lett. 147 (2)*:247-50 (1982); Ramachandran *et al.*, *Hemoglobin 16(4)*:259-66 (1992). Thus, Applicants assert that, in general, proteins are resilient to modification and retain functional activity notwithstanding numerous amino acid substitutions, deletions and insertions.

In addition, Applicants note that the specification teaches assays which can be used to determine whether variants of *tag7* have retained *tag7* activity. Example 5 teaches an *in vitro* method of determining whether *tag7* induces DNA fragmentation. Using this method, one of ordinary skill in the art would also be able to determine if *tag7* variants induce apoptosis. Example 6 teaches an *in vitro* method of determining tumor growth inhibition

induced by *tag7*. Using this method, one of ordinary skill in the art would be able to easily confirm whether *tag7* variants inhibit tumor growth. The experiments mentioned above are routine and easily performed by one of ordinary skill in the art.

In view of the above, it would not require undue experimentation to practice the invention commensurate in scope with the claims. Given a protein's functional resiliency to modification, the guidance provided in the specification as to which particular amino acids are important to the activity and structure of *tag7*, and assays which can be used to determine whether "at least 95% identical" variants have *tag7* activity, Applicants submit that one skilled in the art, enlightened by the teachings of the present application, would be able to routinely make and use the invention commensurate in scope with the claims. Any experimentation necessary to perform the invention would not be undue. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims.

E. Rejection under 35 U.S.C. § 112, First Paragraph

In the Office Action at pages 9-11, the Examiner rejected claims 1-23 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled by the specification. Applicants respectfully traverse this rejection.

The Examiner states that "according to Kiselev, et al (*Journal of Biological Chemistry* **273**: 18633-18639, 1998; Form PTO-1449, citation no. 10-AS), the polynucleotide sequence encoding mouse tag7 protein (GenBank Accession No. X86374; Form PTO-1449, citation no. 11-AT) differs from the polynucleotide sequence, i.e., SEQ ID

NO:1, which the specification teaches encodes mouse tag7 protein." (Paper No. 13, pages 9-10.)

The Examiner further states that "[a]ny inaccuracies in the polynucleotide or polypeptide sequences disclosed in the specification would preclude the successful practice (i.e., production and/or use) of the invention." (*Id.*, page 10) The Examiner also states that "specification apparently offers no disclosure that might explain these discrepancies or serve to instruct the practitioner that the polynucleotide sequences reported elsewhere are considered to be inaccurate. The disclosure, therefore, would not enable the skilled artisan to make and use the claimed invention with a reasonable expectation of success without having to first perform undue experimentation." (*Id.*)

Applicants are aware of the discrepancy between the sequences disclosed in the GenBank report and that disclosed in the patent application. Indeed, the sequences disclosed in the instant application represent the *corrected tag* 7 sequences. Thus, Applicants' disclosure is clearly enabling for nucleic acids and polypeptides comprising the corrected sequences.

Contrary to the Examiner's suggestions, one of ordinary skill in the art fully comprehend that automated DNA sequencing is not error-free, as stated in Applicants' specification:

> as is known in the art for any DNA sequence determined by these approaches, any nucleotide sequence determine herein my contain some errors. Nucleotide sequences determined by such methods are typically at least about 90% identical, more typically at least about 95% identical to at least about 99.9% identical to the actual nucleotide sequence of the sequenced DNA molecule. As is also known in the art, a single insertion or deletion in a determined nucleotide sequence compared to the actual sequence will cause a frame shift in translation of the nucleotide sequence such that the

> predicted amino acid sequence encoded by a determined nucleotide sequence will be completely different from the amino acid sequence actually encoded by the sequence DNA molecule, beginning at the point of such an insertion or deletion.

(Specification, page 14, lines 30-36 and page 15, lines 1-4.) Therefore, an explanation as to the differences in the sequences is unnecessary as one of ordinary skill in the art understands the DNA sequencing methods and possible errors that may be generated.

With respect to Kiselev's disclosure, Applicants note that the sequence disclosed therein differs from that disclosed in the application only at position 463 of Kiselev. Kiselev shows a "C' while the instant application shows a "G". However, both Kiselev and the instant disclosure identify the amino acid corresponding to the codon which includes residue 463 to be a cysteine. Accordingly, it is Applicants' belief that the "C" at position 463 of Kiselev is a typographical error. If it were not, the corresponding amino acid would be a serine and not a cysteine (TCT=Serine). Applicants thus submit that the discrepancy between the sequences represents a typographical error and not a variant sequence. Thus, these facts *in no way* speak to whether or not it would require undue experimentation to practice the claimed invention.

Furthermore, the Examiner states that "with particular regard to claims 1, 5, and 19, while claims 1 and 19 define 'the mature *tag7* polypeptide' as having the amino acid sequence set forth at positions 20 to 182 in SEQ ID NO:2, claim 5 inconsistently defines the mature *tag7* polypeptide as having the amino acid sequence at positions 13 to 182 in SEQ ID NO:2." (Paper No. 13, page 10.) Applicants' recitation of mature *tag7* at amino acids 13 to 182 in SEQ ID NO:2 in claim 5 is a typographical error. The correct mature *tag7* is at amino acids 20 to 182 in SEQ ID NO:2.

Accordingly, the claims are enabled and Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

F. Rejection under 35 U.S.C. § 112, First Paragraph

In the Office Action at pages 11-15, the Examiner rejected claims 1, 2, 4-10 and 12-22 for alleged lack of written description. Applicants respectfully traverse this rejection.

Initially, Applicants note that claims 1, 2, 4-10 and 12-22 have been canceled in favor of new claims. The new claims are generally directed to nucleic acids encoding polypeptides that are 95% identical to a mouse or human *tag7* protein, nucleic acids that are at least 95% identical to the gene encoding human *tag7*, and polypeptides that are 95% identical to a mouse or human *tag7* protein. For the following reasons, Applicants submit that new claims satisfy the requirements of 35 U.S.C. § 112, first paragraph.

The Examiner has stated that "the disclosure of the two isolated species of the claimed genus of nucleic acid molecules, namely SEQ ID NO:1 and SEQ ID NO:3, is considered insufficient to meet to written description requirement." (Paper No. 13, pages 11-12.) Thus, the Examiner has acknowledged that at least one species within the scope of the genus claims is provided in the specification. According to the USPTO's own written description guidelines, the disclosure of "a single species may . . . provide an adequate written description of a generic claim when the description of the species would evidence to one of ordinary skill in the art that the invention includes the genus" and when the species that are described are "representative of the entire genus." (Federal Register, Vol. 66, No. 4, page 1102, 1106, January 5, 2001.) Applicants submit that the disclosure of the specific reference sequences (i.e., SEQ ID NOs:1, 2, 3 and 4), which are members of the claimed

genera, are sufficient to satisfy the written description requirement because the reference sequences are representative of each genus which they are a member of. For example, encoded polypeptides which comprise sequences 95% identical to the reference polypeptides will show *tag 7* activity (e.g., generating antibody capable of binding the full-length *tag 7* protein and/or inducing apoptosis in tumor cells) much like the reference polypeptides. Moreover, members of the genus will share many of epitopic regions of the reference polypeptides. Thus, the polypeptides comprising the specific reference sequences are exemplary of the structure of the variants within the genus. In addition, because the variants have substantially the same nucleotide and/or amino acid sequence as the reference polynucleotides and polypeptides (at least 95% sequence identity), the reference sequences are representative of the sequences that the variants will have. Thus, Applicants assert that the written description requirement has been met because the reference polynucleotides are representative of the genus of claimed polynucleotides. One skilled in the art would recognize that Applicants were "in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (Federal Register, Vol. 66, No.4, page 1106.)

Not only is the species described by Applicants representative of the genus, the description of the species "would evidence to one of ordinary skill in the art that the invention includes the genus." (Federal Register, Vol. 66, No. 4, page 1102.) The specification clearly states that the nucleic acids and proteins of the invention include those which are at least 95% identical to the sequences set forth in SEQ ID NOs:1 and 2, as well as, SEQ ID NOs: 3 and 4. (*See, e.g.,* page 6, lines 15-18 and page 7, lines 5-8.) Thus, one of ordinary skill in the art would plainly recognize, based on Applicants' disclosure, that the

invention includes more than the recited species but also a genus of polynucleotides containing the species.

The Examiner's attention is drawn to the Synopsis of Application of Written Description Guidelines (hereinafter "Synopsis"). Applicants note that the instant claims mirror Example 14 of the Synopsis. Example 14 refers to a claim which reads as follows: "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A→B." According to the example, the specification supporting this claim provides the following information:

> The specification exemplifies a protein isolated from liver that catalyzes the reaction of A→B. The isolated protein was sequenced and was determined to have the sequences as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

(Synopsis, Example 14: Specification.)

Because Applicants' claims (requiring 95% identity to a reference sequence and *tag7* function) are substantially similar to Example 14 and Applicants' specification (teaching methods for making variants and assays for detecting activity) is substantially similar to the specification of Example 14, Applicants' assert that a similar conclusion should be reached about the adequacy of Applicants' written description. The conclusion is that "applicant was in possession of the necessary common attributes possessed by the members of the genus." (Synopsis, Example 14: Analysis.)

The Examiner contends that:

> in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that '[a]n adequate written description of a DNA [molecule] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention'.

(Paper No. 13, page 12.) While Applicants agree that *Eli Lilly* is applicable to the issue at hand, Applicants respectfully disagree that *Eli Lilly* supports a written description rejection of Applicants' claims. The claims at issue in *Eli Lilly* were directed to genetic material using "generic statement[s]" such as "vertebrate insulin cDNA" or "mammalian insulin cDNA." *Lilly*, 119 F.3d at 1568. The Federal Circuit found that these statements were not an adequate description of the genus because the claims described the gene only by what the gene did (functional description), and "did not define any structural features commonly possessed by the members of the genus" such that one skilled in the art could "visualize or recognize the identity of the members of the genus." (*Id.*) In order to satisfy the written description requirement, then, the court held that:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling with in the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.

(*Id.* at 1569.) Thus, the Federal Circuit indicated that the written description requirement for generic claims directed to genetic material, such as cDNA, may be satisfied by providing

the sequences of a representative number of nucleic acids which fall within the scope of the genus *or* by providing a recitation of structural features which are common to a substantial portion of the members of the genus. As indicated above, Applicants assert that, to the satisfaction of the first test set forth in *Eli Lilly*, the reference polynucleotides and polypeptides are representative of the claimed genus. Further, distinct from the claims at issue in *Eli Lilly*, Applicants have not only described the encoded product by what it does, but have described the functional characteristics of the encoded product by reciting epitope-bearing regions of the protein and structural features noted by the composite graph.

Applicants assert that the disclosure of the complete nucleotide and amino acid sequence of the reference sequences, epitopic regions within the reference sequences, and composite graph constitutes a recitation of the structural features common to the members of the genus, which features "constitute a substantial portion of the genus." (*Id.*) That is, the recitation of the amino acid sequences of the reference proteins, for example, is a recitation of the structural features common to the members of the genus because the proteins included within the genus will have at least 95% of their amino acid sequence (primary structure) in common with each other (and to the reference proteins).

Further, the reference polynucleotides and polypeptides may share in common with the other members of the genus specific epitopic regions capable of generating antibody. Moreover, one skilled in the art would be able to "visualize and recognize" innumerable members of the genus given the disclosure of the reference nucleotide and amino acid sequences and the location and characterization of important regions within these sequences. Thus, Applicants assert that the specification has satisfied the requirements for written description as set forth in *Eli Lilly*.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdrawal the rejection.

G. Rejection under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 15-18, the Examiner rejected claims 1-23 as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner has rejected claims 1-7 and 9-18 as allegedly indefinite for failing to clearly define the fragment of the nucleotide. Solely to advance prosecution and not in acquiescence to the Examiner's rejection, claims 1-7 and 9-18 have been cancelled in light of new claims 53-93. The new claims do not recite the language in which the Examiner rejects. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 1-7 and 9-18 as allegedly indefinite because claim 1 recites the phrase "the mature tag7 polypeptide having the amino acid sequence at positions 20 to 182 of SEQ ID NO:2" while claim 5 recites, "the mature tag7 polypeptide having the amino acid sequence at positions 13 to 182 in SEQ ID NO:2." The Examiner has asserted that the claims are "incongruous." As previously stated, the portions of the specification which indicate that the mature *tag7* polypeptide has an amino acid sequence of 13 to 182 in SEQ ID NO:2 was an error. The new claims do not recite the error. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 1-7 and 9-18 as allegedly indefinite because claim 1 recites the term "a tag7-encoding polypeptide" in lines 9 and 12. Solely to advance prosecution and not in acquiescence to the Examiner's rejection, claims 1-7 and 9-18 have been cancelled in light of new claims 53-93. The new claims do not recite the language in which the Examiner rejects. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 8-18 and 20-23 as allegedly indefinite because claim 18 recites the word, "about." Solely to advance prosecution and not in acquiescence to the Examiner's rejection, claims 8-18 and 20-23 have been cancelled in light of new claims 53-93. The new claims do not recite the language in which the Examiner rejects. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 10, 11, 14-18, and 20-23 as allegedly indefinite because claim 10 recites the limitation "wherein said nucleic acid molecule is isolated from a human." The Examiner states that "[r]ecitation of the limitation renders the claim indefinite because the nucleic acid to which claim 8 refers, i.e., the nucleic acid molecule encoding an epitope bearing portion of SEQ ID NO:2, is derived from the sequence of a nucleic acid molecule isolated from a mouse." (Paper No. 13, page 17.) Solely to advance prosecution and not in acquiescence to the Examiner's rejection, claims 10, 11, 14-18, and 20-23 have been cancelled in light of new claims 53-93. The new claims do not recite the language in which the Examiner rejects. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 19-23 as allegedly indefinite because claim 19 recites the phrase "a fragment thereof" in line 15. Solely to advance prosecution and not in acquiescence to the Examiner's rejection, claims 19-23 have been cancelled in light of new claims 53-93. The new claims do not recite the language in which the Examiner rejects. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has rejected claims 19-23 as allegedly indefinite because claim 19 recites the phrase "the mature tag7 polypeptide having the amino acid sequence as set forth at positions 20 to 182 of SEQ ID NO:2" while claim 5 recites, "the mature tag7 polypeptide having the amino acid sequence at positions 13 to 182 in SEQ ID NO:2." The Examiner has asserted that the claims are "incongruous." As previously stated, the portions of the specification which indicate that the mature *tag7* polypeptide has an amino acid sequence of 13 to 182 in SEQ ID NO:2 was an error. The new claims do not recite the language in which the Examiner rejects. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

H. Priority Issue

Claims 1, 2, and 5-23 have been cancelled in favor of new claims 53 to 93. The new claims have support in the specification of U.S. Application No. 08/893,764 (hereinafter "the '764 application"). Specifically, support in the '764 application for new claims 53-72 and 93 may be found at page 4, lines 8-28; page 5, lines 11-30; page 6, lines 1-25; page 7, lines 5-6; page 8, lines 19-20; page 44, lines 2-26; page 60, lines 15-25; Figures 1 and 2; and in Examples 5 and 6. Applicants emphasize that the initial disclosure of the full length

nucleotide and polypeptide of murine *tag7* is in the '764 application. Accordingly, the new claims are entitled to the filing date of the '764 priority application.

I. Rejections under 35 U.S.C. §§ 102/103

In the Office Action at pages 18-23, the Examiner has rejected the original claims under 35 U.S.C. §§ 102(a) or 102(b) or, in the alternative, § 103(a). Applicants respectfully traverse these rejections with respect to the new claims, in view of the foregoing amendments and the following remarks.

A. The Rejection over WO 97/29765 A1

In the Office Action at pages 19-20, the Examiner rejected claims 1, 2, 6-9 and 12-21 under 35 U.S.C. § 102(a) as allegedly anticipated by or, in the alternative, § 103(a) as allegedly obvious over WO 97/29765 A1. Applicants respectfully traverse these rejections.

Based on the face page information, WO 97/29765 was published on August 21, 1997. Since Applicants' earliest priority date is July 11, 1997 (U.S. Application No. 08/893,764, now U.S. Patent No. 6,172,211), WO 97/29765 cannot properly be cited in a rejection under 35 U.S.C. §§ 102(a) or, in the alternative, 103(a) as its' publication date is not before the filing date of Applicants' priority application. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

B. The Rejection over Kustikova Documents

In the Office Action at pages 20-21, the Examiner rejected claims 1, 2, 6-9 and 12-14 under 35 U.S.C. § 102(b) as allegedly anticipated by or, in the alternative, §103(a) as

allegedly obvious over Kustikova *et al.*, *Genetika 32*:621-628 (1996) (hereinafter "K1"), Kustikova *et al.*, *Russian J. Genetics 32*:540-546 (1996) (hereinafter "K2") and Kustikova *et al.*, GenBank Accession No. X86374, created on April 18, 1995 (hereinafter "K3"). Applicants respectfully traverse these rejections.

Applicants note that K2 is an English language translation of K1 and therefore the two documents disclose identical sequences. K3 is also identical to K1 and thus, K2. The new claims are generally directed to nucleic acids encoding polypeptides that are 95% identical to a mouse or human *tag7* protein, nucleic acids that are at least 95% identical to the gene encoding human *tag7*, and polypeptides that are 95% identical to a mouse or human *tag7* protein. Neither K1, K2 nor K3 teach or suggest the subject matter of the new claims. Accordingly, neither K1, K2 nor K3 anticipate or render obvious the claimed invention.

Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

C. The Rejection over Prokhortchouk

In the Office Action at pages 21-22, the Examiner rejected claims 1, 2, 6-9, 12-13 and 19-21 under 35 U.S.C. § 102(b) as allegedly anticipated by or, in the alternative, § 103(a) as allegedly obvious over Prokhortchouk *et al.*, GenBank Accession No. Y12088, created on April 1, 1997 (hereinafter "Prokhortchouk"). Applicants respectfully traverse these rejections.

In an effort to advance prosecution, claims 1, 2, 6-9, 12-13 and 19-21 have been cancelled in favor of new claims 53-93. Prokhortchouk does not teach or suggest the subject matter of the new claims which are generally directed to nucleic acids encoding polypeptides

that are 95% identical to a mouse or human *tag7* protein, nucleic acids that are at least 95% identical to the gene encoding human *tag7*, and polypeptides that are 95% identical to a mouse or human *tag7* protein. Accordingly, Prokhortchouk does not anticipate or render obvious the claimed invention.

Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

D. The Rejection over Kang

In the Office Action at pages 22-23, the Examiner rejected claims 1, 2, 6-9, 12-13 and 19-21 under 35 U.S.C. § 102(a) as allegedly anticipated by or, in the alternative, § 103(a) as allegedly obvious over Kang *et al.*, GenBank Accession No. AF076482, created on July 8, 1998 (hereinafter "Kang"). Applicants respectfully traverse these rejections.

The GenBank database shows that Kang was created on July 8, 1998. Since Applicants' earliest priority date is July 11, 1997 (U.S. Application No. 08/893,764, now U.S. Patent No. 6,172,211), Kang cannot be properly cited in a rejection under 35 U.S.C. § 102(a) or § 103(a) as its' publication date is not before the filing date of Applicants' earliest priority application.

Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

J. The Statutory Double Patenting Rejection

In the Office Action at pages 23-24, the Examiner rejected claims 3 and 4 under 35 U.S.C. § 101, based on commonly-owned U.S. Patent No. 6,172,211 B1. Applicants traverse this rejection.

Claims 3 and 4 have been cancelled in light of claims 53-93. Therefore, this rejection is rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

K. The Non-statutory Double Patenting Rejection

In the Office Action at pages 24-25, the Examiner rejected claims 1-22 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-10 of commonly-owned U.S. Patent No. 6,172,211 B1. Applicants respectfully request that this rejection be held in abeyance until the claims are found to be allowed.

Conclusion

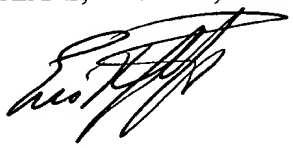
All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Eric K. Steffe
Attorney for Applicants
Registration No. 36,688

Date: 6/14/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the Specification:

At page 1, after the title and before the first line of text on page 1, please insert the following paragraph:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Phase of International Application No. PCT/EP98/04287, filed July 10, 1998, published in English as WO 99/02686 on January 21, 1999, and a continuation-in-part of U.S. Application No. 08/893,764, filed July 11, 1997, now U.S. Patent No. 6,172,211.

Substitute the paragraph beginning on page 49, line 14, with the following paragraph:

One such fragment isolated and characterized here is the tag 7 gene which exhibits a very high level of transcription in the liver-metastasizing VMR-L tumor (see Figure 2). Sequence analysis showed that the PCR fragment was flanked on both sides by the 5' terminal primer 5'-AATCGGGCTG-3' [(SEQ ID NO:4)] (SEQ ID NO:6). When the nucleotide sequence of a cDNA clone from the total VMR-L cDNA library was analyzed, a sequence which is homologous to this primer over a length of eight bp was found at a distance of 52 nucleotides from the 3' poly A+ tail of the cloned cDNA. It is likely that the traditional oligo-dT primer could be used in the "differential RNA display" technique instead of the 3' terminal primer, and only the 5' terminal primers could be varied; such an approach would probably decrease the number of fragments obtained, but would simultaneously increase the resolving capacity of the gel.

Substitute the paragraph beginning on page 56, line 24, with the following paragraph:

Differential display of mRNA was performed by the standard technique (Liang, P., and Pardee, A.B., Science 257:967-971 (1992)). Briefly, cDNA was obtained from 0.2 μg of mRNA by the reverse transcription reaction using the T12 AC primer (5'-TTTTTTTTTTTTAC-3') [(SEQ ID NO:3)] (SEQ ID NO:5) and Moloney Murine Leukemia Virus (M-MuLV) reverse transcriptase. T12AC and two short random 5' oligonucleotide primers (primer 1:5'-AATCGGGCTG-3' [(SEQ ID NO:4)] (SEQ ID NO:6); primer 2: 5'-AGTCAGCCAC-3' [(SEQ ID NO:5)] (SEQ ID NO:7)) were used as the 3' primers in two different combinations in the course of the polymerase chain reaction (PCR). Amplified cDNAs were separated by electrophoresis in 6% polyacrylamide gels containing 7 M urea.

Substitute the paragraph beginning on page 81, line 14, with the following paragraph:

One such fragment isolated and characterized here is the tag7 gene which exhibits a very high level of transcription in the liver-metastasizing VMR-L tumor (see Figure 2). Sequence analysis showed that the PCR fragment was flanked on both sides by the 5' terminal primer 5'-AATCGGGCTG-3' [(SEQ ID NO:4)] (SEQ ID NO:6). When the nucleotide sequence of a cDNA clone from the total VMR-L cDNA library was analyzed, a sequence which is homologous to this primer over a length of eight bp was found at a distance of 52 nucleotides from the 3' poly A+ tail of the cloned cDNA. It is likely that the traditional oligo-dT primer could be used in the "differential RNA display" technique instead of the 3' terminal primer, and only the 5' terminal primers could be varied; such an approach would probably decrease the number of fragments obtained, but would simultaneously increase the resolving capacity of the gel.

In the Claims:

Claims 1-52 are cancelled.

New claims 53-93 are added.